Documented Symptomatic Hypoglycaemia in Children and Adolescents Using Multiple Daily Insulin Injection Therapy

S. Tupola*[1,2], J. Rajantie[2,3]

[1]*Aurora Hospital, Helsinki, Finland*
[2]*Children's Hospital University of Helsinki, Helsinki, Finland*
[3]*Jorvi Hospital, Espoo, Finland*

Symptomatic episodes of documented hypoglycaemia were characterized with the aid of a 3-month diary in a single-centre, unselected group of 161 children and adolescents with Type 1 diabetes mellitus, treated mainly (81 %) with multiple-dose insulin therapy. Patients and families were asked to write in the diary all the symptomatic episodes in which blood glucose concentration proved to be $\leqslant$3 mmol l^{-1} before treatment. Of the patients, 83 (52 %) had a total of 287 hypoglycaemic episodes (0.6 attack per month per patient). The majority of the attacks, 221 (77 %), were mild (patients $\geqslant$6 years able to treat themselves). Only two attacks were severe, resulting in coma and/or convulsion. The most common dominant symptoms were weakness (29 %), tremor (20 %), hunger (14 %), and drowsiness (12 %). Of all the dominant symptoms, 39 % were classified as autonomic, 20 % neuroglycopenic, and 41 % non-specific. In children under 6 years, autonomic symptoms were less common than in adolescents 15 years or over (34 % vs 57 %, $p = 0.01$). In conclusion, the incidence of documented symptomatic hypoglycaemia was low. The symptoms were more often neuroglycopenic or non-specific than autonomic, especially in young children. © **1998 John Wiley & Sons, Ltd.**

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Introduction

Hypoglycaemia is the most common acute complication of the treatment of Type 1 diabetes mellitus. Activation of the autonomic nervous system and, later, progressive impairment of neurological function cause its presenting symptoms.[1] Because similar signs may occur with a normal or even an elevated blood glucose level, blood glucose concentration should be measured, if possible, to confirm the hypoglycaemia.[2–4] Despite the fact that self-blood glucose monitoring (SBGM) is already routine in the daily follow-up of Type 1 diabetes, many patients and their parents do not check the blood glucose level when the patient experiences symptoms believed to be due to hypoglycaemia. However, valid information on the symptoms associated with true hypoglycaemia in everyday life can only be obtained by using SBGM.

The few studies on the frequency and clinical associations of symptomatic hypoglycaemia in children with diabetes are based on questionnaires without SBGM,[5,6] or on a small study population.[7] The majority of the patients in these studies were treated twice a day with insulin.

We have now studied SBGM-verified symptomatic hypoglycaemic attacks in a large, population-based, single-centre group of children and adolescents with Type 1 diabetes mellitus, treated mainly with multiple daily insulin injection therapy ($\geqslant$3 insulin injections per day).

Patients and Methods

Patients

All children and adolescents who had had Type 1 diabetes mellitus for at least 6 months were enrolled in the study during their scheduled visit at the Aurora Hospital diabetes outpatient clinic. This clinic is responsible for the care of 95 to 97 % of young people with diabetes in the city of Helsinki. Of 198 patients, 161 (81 %) completed the study, by returning the hypoglycaemia diary. Their clinical data at the beginning of the study are given in Table 1. The 37 non-responders did not differ significantly from the participants with respect to age, gender, duration of diabetes, HbA_{1c} levels or daily insulin dosage. Of the patients in the study, 81 % received insulin in three or more daily doses. All

*Correspondence to: Dr S. Tupola, Veininmaki 1B, FIN-02620 Espoo, Finland
Sponsors: Foundation for Paediatric Research, Finland

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Table 1. Clinical data for the 161 patients completing the 3-month hypoglycaemia diary

Age (yr)[a]	13.1 (2.5–21)
Gender (F/M)	81/80
Duration of diabetes (yr)[a]	4.2 (0.5–18.6)
HbA_{1c}(%)[b]	9.0 ± 1.7
Insulin dose (U $kg^{-1}day^{-1}$)[b]	0.8 ± 0.2
⩾3 insulin injections per day (%)	81

Data shown as [a]median (range), [b]mean ± SD.

patients owned a blood glucose meter (nine different types of meters, lower reference limits 0–2.2 mmol l^{-1}).

Methods

An experienced nurse interviewed patients and families regarding their habits of SBGM in hypoglycaemic situations. Each patient's insulin regimen and daily insulin dose (U kg^{-1}) were registered. Blood was taken for measurement of HbA_{1c}. Thereafter, a hypoglycaemia diary was given to patients and families for use during the next 3 months. They were asked to complete a diary entry in all situations involving symptoms of hypoglycaemia as soon as possible, but at most within 24 h, after the episode. Patients and their parents were asked to confirm, if possible, all hypoglycaemia-suspected symptoms or signs by means of blood glucose measurement. Only the episodes in which blood glucose concentration was verified to be ⩽3 mmol l^{-1} were included in the diary and in the analysis.

We gave no symptom lists to the patients and their families. Dominant symptoms or signs were to be described in their own words. In addition, treatment and all events associated with hypoglycaemia (insulin injections, meals and snacks, exercise, possible special situations such as travel, and diseases other than diabetes within the preceding 24 h) were to be recorded. Three months after returning the diary, patients and families were interviewed again on their SBGM habits, and the same variables were registered as at the first visit. Patients 15 years or over were interviewed without their parents, but were asked to fill in the diary with their parents. Younger patients participated in the study with their parents. If the aid of a person other than their own parent was needed in a hypoglycaemic situation, the patients and parents were asked to fill in the diary with that person. Data from each patient were confirmed by review of that patient's hospital record. The study was approved by the local medical ethics committee. Oral consent was obtained from all parents (guardians) of the patients under 15 years, as well as from the patients 7 years or over (school-starting age in Finland).

Symptomatic hypoglycaemia was classified into three degrees of severity—mild, moderate, and severe—according to the consensus guidelines for the management of Type 1 diabetes in childhood and adolescence.[8] In mild hypoglycaemia, the patient is able to detect and treat the hypoglycaemia by him/herself. In moderate hypoglycaemia, the help of another person is needed, so all but severe hypoglycaemic episodes in patients younger than 6 years were included; severe hypoglycaemia leads to unconsciousness and/or convulsion. In this study, the most dominant symptoms (one per episode) were classified as: (1) autonomic, adrenergic or cholinergic, (2) neuroglycopenic, and (3) non-specific[9] as shown in Table 2. Blood glucose levels for symptom–profile analysis (<2.2 mmol l^{-1} and 2.8–3.0 mmol l^{-1}) were chosen according to the hierachy of glycaemic thresholds for symptoms in healthy human adults.[10] HbA_{Ic} was analysed by high pressure liquid chromatography, non-diabetic range: 4.2–6.6%.

Student's *t*-test, a paired *t*-test, χ^2-test, Fisher's exact test, and a median test were used, where appropriate, for statistical analysis. A *p*-value of <0.05 was considered significant.

Results

Of the 161 patients who completed the diary, 83 (52 %) experienced a total of 287 SBGM-verified symptomatic hypoglycaemic episodes during the 3-month study period, giving an average incidence of symptomatic hypoglycaemia of 0.6 attack per month per patient. In the group of patients under 6 years, 12/17 (71 %) had a total of 58 episodes, a rate of 1.1 attacks per month per patient. The majority of the attacks, 221 (77 %), were mild, and 64 (22 %) were moderate (58 occurring in children under 6 years). If these children had been at least 6 years old, their episodes classified as moderate may have been classifiable as mild. Of all the attacks, only 2 were severe, giving an event rate of 4.9/100 patient-years.

Table 2. Dominant symptoms or signs in 287 episodes of documented hypoglycaemia among 83 patients

	Mild episodes *n* = 221	Moderate episodes *n* = 64	Severe episodes *n* = 2
Autonomic symptoms			
Tremor	48	10 (9[a])	
Hunger	32	9[a]	
Sweating	9	3 (2[a])	
Neuroglycopenic symptoms			
Drowsiness	15	19 (17[a])	
Irritability/aggressiveness	9	1[a]	
Dizziness	3	5[a]	
Poor concentration	3		
Blurred vision	2		
Slurred speech		1	
Convulsion			1
Non-specific symptoms			
Weakness	75	7[a]	
Nausea	15		
Abdominal pain	5	2[a]	
Headache	4		
Tearfulness	1	7 (6[a])	1

[a]Patients < 6 years, *n* = 58.

SBGM-readings gave the display 'low', indicating that the blood glucose value had been below 2.2 mmol l^{-1}, in 52 attacks. In the remaining 235 attacks, the blood glucose concentration (mean ± SD) was 2.5 ± 0.3 (range 1.3–3.0) mmol l^{-1}.

The most common dominant symptoms were weakness (29 %), tremor (20 %), hunger (14 %), and drowsiness (12 %) (see Table 2). Of the symptoms, 39 % were classified as autonomic, 20 % neuroglycopenic, and 41 % non-specific. Patients' age, diabetes duration, and HbA_{1c} were similar in these symptom groups. However, in a comparison of the dominant symptoms in children under 6 years ($n = 58$) with those in adolescents 15 years or over ($n = 58$), the younger children had less autonomic (34 % vs 57 %, $p = 0.01$), but similarly non-specific symptoms or signs (26 % vs 31 %, $p = 0.5$, respectively). The most common symptom in children under 6 years was drowsiness (29 %), but in adolescents 15 years or over it was tremor (41 %). In the two severe attacks, the presenting symptom before unconsciousness was convulsion in one and tearfulness in the other.

Of the 75 very low blood glucose measurements (<2.2 mmol l^{-1}), 67 (89 %) were in patients aged 6 years or over. The 75 episodes with blood glucose <2.2 mmol l^{-1} had a similar distribution of symptom groups as those 71 with a blood glucose value 2.8–3.0 mmol l^{-1}, with autonomic symptoms being the most frequent (40 % in those with blood glucose <2.2 mmol l^{-1} vs 44 % with 2.8–3.0 mmol l^{-1}, $p = 0.7$). Neither were there any significant age-dependent differences in symptom profiles at these blood glucose ranges.

Predisposing causes, as remembered by patients or their families, were given in 58 % of the cases. The most frequent causes were inadequate food intake or delayed meal (25 %) and unusual extra exercise (20 %) (Table 3). Most of the attacks (58 %) occurred in the afternoon or in the evening, 29 % in the morning and 8 % at night. Of the 24 night attacks, 8 were thought to be due to extra physical exercise, but in 11, no predisposing cause was given.

Of all the attacks, 98 % were treated without any medical aid from health professionals. Two moderate attacks were treated in hospital, and in three (one mild, one moderate and one severe) a phone call to hospital was made immediately after the attack. Treatment was intravenous glucose in two moderate attacks, intramuscular glucagon in the one severe attack, and oral carbohydrate in the rest of the attacks.

Table 3. Suggested predisposing causes for 287 episodes of symptomatic hypoglycaemia among 83 patients

	Mild episodes $n = 221$	Moderate episodes $n = 64$	Severe episodes $n = 2$
Inadequate food intake/delayed meal	57	16 (15[a])	
Unusual extra exercise	43	15 (13[a])	1
Excess intake of insulin	10	6[a]	
Acute gastroenteritis	9	9 (8[a])	
Late bedtime with alcohol use	1		
No obvious reason	101	18 (16[a])	1

[a]Patients < 6 years, $n = 58$.

At the beginning of the study, the patients who later experienced symptomatic hypoglycaemia had lower HbA_{1c} levels than those who did not (8.6 ± 1.5 vs 9.3 ± 1.8 %, $p = 0.01$, 95 % confidence interval (CI) for difference in mean values 0.03–1.38). There were no significant differences between these two groups in age, gender, diabetes duration, daily insulin dose or insulin regimen.

Prior to the study, 40 % of the patients and their families were accustomed to measuring blood glucose before ingestion of an extra snack in hypoglycaemic situations. Three months after returning the 3-month diary, this percentage rose to 52. Confirmation of hypoglycaemia with SBGM had thus increased significantly ($p = 0.03$). Simultaneously, HbA_{1c} had decreased in the whole study population from 9.0 ± 1.7 % to 8.7 ± 1.6 % (mean ± SD, $p = 0.04$, 95 % CI for the difference in mean values 0.11–0.49), and in the group with symptomatic hypoglycaemia 8.6 ± 1.5 % to 8.3 ± 1.3 % ($p = 0.02$; 0.03–0.53).

Discussion

In this prospective study of young patients treated mainly by multiple daily insulin injection therapy, the incidence of both mild and severe symptoms of hypoglycaemia was quite low. This might in part be explained by our strict criteria for a symptomatic hypoglycaemic episode: any such attack had to be verified by SBGM (blood glucose ⩽3 mmol l^{-1}). Some symptomatic episodes might have been excluded because of the lack of SBGM. In this study, we did not collect data on symptomatic episodes with blood glucose >3 mmol l^{-1}. On the other hand, had SBGM not been demanded, non-hypoglycaemic episodes would have been included. Low frequencies of symptomatic hypoglycaemia have been reported in conventionally treated patients.[5,7] Åman *et al.*,[6] reporting a higher incidence in their patients, of whom 55 % received insulin in three or more daily doses, related this incidence to the intensive insulin therapy: HbA_{1c} levels in their whole study population, however, were higher than in our patients. In the present study, the rate of severe hypoglycaemia (4.9/100 patient-years) is in accordance with our results concerning incidence of severe hypoglycaemia in our ongoing 2-year prospective study.

The most common dominant hypoglycaemic symptoms were weakness, tremor, hunger, and drowsiness. Of all the symptoms, 39 % in all patients, and only 34 % in children under 6 years, were classified as autonomic adrenergic or cholinergic, which are traditionally regarded as primary warning symptoms of hypoglycaemia and are attributed to hormonal counterregulatory mech-

anisms. In adults with Type 1 diabetes, this proportion has been reported to be much higher,[11,12] as it was in our adolescents 15 years or over. McCrimmon *et al*.[13] interviewed children with diabetes and their parents regarding symptoms of hypoglycaemia, and found that symptoms in young children differ from those experienced by adults and include a smaller proportion of autonomic changes. Our study confirms these findings. However, it has been shown that children with diabetes have greater catecholamine responses to hypoglycaemia than do adults.[14,15] Therefore, the predominance of neuroglycopenic symptoms in children cannot be explained by defective counterregulation, but maybe due to the transition from sympathetic to neuroglycopenic manifestations being more rapid in children than in adults.[16,17] In our patients, we could find no difference in symptom profiles when comparing the blood glucose level thought to be associated with neuroglycopenia (<2.2 mmol l^{-1}) to the level with probable autonomic manifestations (2.8–3.0 mmol l^{-1}).[10] Both the young children and the adolescents quite frequently experienced symptoms which could not be classified as autonomic or neuroglycopenic, but were non-specific. McCrimmon *et al*.[13] also found that non-specific symptoms or signs are important features of hypoglycaemia in children with Type 1 diabetes. The aetiology of these non-specific symptoms is unclear.

Patients and their families described predisposing causes for 58 % of the hypoglycaemic episodes. As in other series, inadequate food intake/delayed meal and unusual extra exercise were thought to be the most common causes.[6,7] Somewhat higher percentages of obvious predisposing factors have been reported for severe hypoglycaemia in children with diabetes.[18,19] Extra physical exercise on the preceding day was thought to be the predisposing cause in one-third of our patients' nocturnal attacks. Delayed hypoglycaemic reactions associated with exercise should be among the topics emphasized in patient education.

Of our patients' symptomatic hypoglycaemic episodes, only 8 % were nocturnal, but we only recorded symptomatic episodes. Conventionally treated children have been reported to experience symptomatic nocturnal attacks more frequently than this.[6,7] Studies concerning nocturnal glucose profiles in children with Type 1 diabetes have shown unacceptably high hypoglycaemia rates, most episodes however being asymptomatic.[20,21]

Three months after the study our patients reported that they were now accustomed to confirming hypoglycaemic symptoms with SBGM more frequently. Their glycaemic control had also improved. Perhaps some patients who had previously based their behaviour on subjective estimates of blood glucose had noted how unreliable this can be. However, it is possible that these results are only short-term consequences of our study intervention.

In conclusion, documented hypoglycaemic symptoms of children with Type 1 diabetes differ from those experienced by adults and dominant features more often include neuroglycopenic and non-specific rather than autonomic symptoms. This finding is particularly pronounced in younger children. Parents and care-givers should be made aware of the relative obscurity of hypoglycaemic symptoms and signs in children.

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